

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing

(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference

see form PCT/ISA/220

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US2004/008459

International filing date (day/month/year)

19.03.2004

Priority date (day/month/year)

24.03.2003

International Patent Classification (IPC) or both national classification and IPC

C07D311/86, C07D405/04, C07D219/06, C07D219/16, C07D401/06, C07F9/655, C07F9/64, C07D405/12,

Applicant

ICOS CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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(1/24/05)

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/008459

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/008459

Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/008459

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 30-34

because:

☒ the said international application, or the said claims Nos. 30-34 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/008459

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	22
	No: Claims	1-21,23-34,40-45
Inventive step (IS)	Yes: Claims	22
	No: Claims	1-21,23-45
Industrial applicability (IA)	Yes: Claims	1-29,35-45
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

- 1) The present application relates to substituted xanthenes, thioxanthenes and acridinones with DNA-PK inhibiting activity and their applications.

2) Cited documents

D1: WO 02/20500 A
D2: ARZNEIMITTEL-FORSCHUNG, vol. 49, no.3, pages 259-266,
D3: WO 92/16517 A
D4: FARMACO, vol. 54, no. 6, pages 411-415,
D5: DE 31 41 970 A
D6: WO 96/16632 A
D7: DATABASE CAPLUS STN; DN:110150323
D8: WO 01/17985 A
D9: US 2001/027210 A1
D10: TETRAHEDRON, vol. 49, no. 19, 1993, pages 4127-4134,
D11: DATABASE CAPLUS STN; DN:136:197028
D12: TETRAHEDRON, vol. 57, no. 44, pages 9131-9135,
D13: DATABASE CAPLUS STN; DN: 78:124471 1973
D14: DATABASE CAPLUS STN; DN: 70:96661
D15: EP-A-0 471 516
D16: WO 90/14008 A
D17: JP 11 199565 A (PAJ-Abstract)
D18: J.MED.CHEM., vol. 42, no. 12, pages 2136-2144,
D19: ARZNEIM.-FORSCH., vol. 40, no. 9, 1990, pages 1026-1029,
D20: US-A-4 539 412
D21: J.MED.CHEM., vol. 23, pages 1329-1333
D22: US-A-3 904 631
D23: J.MED.CHEM., vol. 39, no. 9, pages 1857-1863.

3) Clarity

It is observed that claims 1-8 and 11-21 relate to a group of compounds for which a preliminary search indicated that it covers a multitude of known compounds, including compounds known for use in cancer therapy (see item Novelty below) such that it is not evident for which subject-matter protection can validly be sought. In view of this multitude of known compounds only a representative selection of relevant documents has been presented in the search report. Moreover, it is observed that claims 11-21 lack clarity to such an extent that a meaningful search could not be performed for the defined matter. In this context it

is observed that claim 11-19 refer to a formula comprising R3 and R4 whereas the following definitions only refer to R1 and R2 and dependent claims 20-21 refer to a formula with R1. Moreover, claim 21 refers to a compound of claim 20 in which A is absent, which would leave an incomplete structure.

4) Novelty

Document D1 describes DNA-PK inhibitors of general formulae (I) and (II) (see pages 5/7) which resemble the compounds presently defined (note that R1/R2 and R5 and R6 may form fused rings); the tricyclic compounds presently defined are however not specifically disclosed.

Documents D2-D23 describe a variety of compounds falling under the presently defined compounds, including compounds with anti-cancer activity.

In this context it is observed that the functional feature in the present claims as to compounds with DNA-PK inhibiting activity is not considered to delimit the claimed matter from the compounds in the prior art unless the applicant is able to show that the known compounds would not exhibit such activity. In such case, it would however be questionable whether the person skilled in the art would be able to reduce the defined subject matter to practice without undue burden (clarity/sufficiency).

5) Inventive step

In as far as the subject-matter is new, the following observations apply as to the requirement of inventive step.

- 5.1 The application states specifically that a particular compound covered by the present claims (10-benzyl-1-hydroxy-3-morpholin-4-yl-10H-acridin-9-one) is an effective agent in DNA-PK inhibition assays (see e.g. page 75) and indicates that further compounds have been tested. Document D1 seems in this context to represent the closest prior art describing structurally related compounds with similar activity/utility. Accordingly, the problem underlying the present subject-matter seems the provision further DNA-PK inhibitors.

As solution to such a problem the claimed matter would not seem obvious to person skilled in the art; even though document D1 indicates that the relevant activity is maintained in compounds with a fused ring core structure, the tricyclic core structure of the presently defined compounds is not covered by the teaching of D1 nor does any further prior art suggest that the DNA-PK inhibiting activity

would be preserved in such tricyclic compounds.

- 5.2 It is however observed, that the activity for the defined compounds is substantiated only to a very limited extend: only for a single specific compound activity is stated whereas also the further examples relate to a very limited subgroup of compounds within the subject-matter claimed. Considering the basis on which an inventive step is acknowledged in item 5.1 (structural differences with compounds D1), it is on the same basis not considered evident from the limited substantiation of activity that the claimed matter will generally solve the relevant problem. Merely as new compounds with potential pharmaceutical activity, the claimed matter would not seem to involve an inventive step in view of the known compounds with anti-cancer activity as for instance mentioned in documents D2, D3, D8, D9, D15, D16, D18, D20 and D21.

- 6) Further observations
Claims 30-34 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

The structure in example 10 seems incorrect.

The example 44 seems not covered by the claims.